Influence of intracoronary nifedipine on left ventricular function, coronary vasomotility, and myocardial oxygen consumption

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SUMMARY The effect of intracoronary nifedipine on regional and global left ventricular performance, coronary vasomotility, and myocardial oxygen consumption is reported. Left ventricular pressures and volume indices of contractility and relaxation were simultaneously recorded in five patients without coronary artery disease. In these patients, nifedipine in the left main coronary artery not only delayed (+115 ms) anterior wall contraction but also slowed (3·5 vs 1·9 cm/s) and depressed it (−26%), resulting in a depression of global left ventricular ejection. This asynchrony and depression of regional contraction is considered to be responsible for the slowed isovolumic contraction and relaxation of the whole ventricle. In 10 other patients with coronary artery disease, coronary sinus blood flow and myocardial oxygen consumption were measured before and after intracoronary nifedipine. The observed decrease in myocardial oxygen consumption (−28%) depended primarily on a decrease in contractility and left ventricular performance. In a third study group of 12 patients with coronary artery disease, the effects of intracoronary nifedipine on the coronary vasomotility of 40 coronary segments (normal, prestenotic, stenotic, poststenotic) were quantitatively determined. Left ventricular haemodynamics and coronary sinus saturation were monitored while the cineangiograms were recorded before and after nifedipine. Nifedipine provoked vasodilatation of the normal (+10·3%), prestenotic, stenotic (+4 to 30%), and poststenotic (+16·4%) coronary segments, which persisted after the disappearance of its direct effects on the myocardium. This transient regional "cardioplegic" effect of nifedipine, associated with an increase in coronary blood flow, a reduction in myocardial oxygen consumption, and a vasodilatation of the epicardial vessels is likely to be beneficial during temporary coronary occlusion such as occurs in spasm or transluminal angioplasty.

Direct intracoronary injection of nifedipine is used increasingly in an effort to reverse spontaneously occurring or induced spasm[1][2] and to restore coronary blood flow. Recently introduced techniques, such as transluminal angioplasty and fibrinolytic recanalisation of coronary artery thrombosis have also become indications[3][4] for injecting nifedipine directly into the affected coronary artery, since it is argued that the specific inhibitory action of nifedipine on contractile energy expenditure may favourably influence the

oxygen supply/demand ratio for ischaemic or potentially ischaemic cardiac cells in the affected region.

Because of the potential value of this drug, it is necessary to determine to what extent selective intracoronary bolus injection depresses left ventricular performance in man and/or reduces the myocardial oxygen consumption while at the same time dilating the coronary artery system.

Patients and methods

PATIENT AND DESIGN OF STUDY
For the first part of the study, five patients (32 to 55 years) were catheterised because of suspected coronary artery disease. Four had atypical chest pain and

one had exertional angina, but all proved to have normal coronary arteries, with ejection fractions well within the normal range. One patient, however, had asymmetrical septal hypertrophy without outflow obstruction and one had electrocardiographic evidence of left ventricular hypertrophy without strain.

Pressures were recorded with a tip-manometer mounted on an 8 F catheter*. Derived variables were calculated on line by a computer system.[5] A 30° right anterior oblique ventriculogram (50 frames per second) was obtained by injection of 0·75 ml/kg 76% Urografin†. When diagnostic coronary arteriography showed normal coronary arteries, informed consent was obtained for the remainder of the study. This included an additional left ventricular cineangiogram 30 seconds after a bolus injection of 0·075 to 0·175 mg nifedipine into the left main coronary artery. The injection was made no sooner than 20 minutes and only after left ventricular end-diastolic pressure and the contractility variables were identical with those recorded before the initial angiogram.

The patient's position was kept unchanged in relation to the x-ray equipment during both angiograms. Movement of the diaphragm was excluded by shallow inspiration, taking care to prevent the Valsalva manoeuvre.

ANALYSIS OF ISOVOLUMIC INDICES DURING VENTRICULOGRAPHY
The on-line computer system provides the following data: peak left ventricular pressure (mmHg), left ventricular end-diastolic pressure (mmHg), and peak positive rate of change of pressure (pk+dP/dt in mmHg/s). In addition, isovolumic relaxation phase variables were calculated: peak negative rate of change of pressure (pk−dP/dt) and the time constant of relaxation (T) by the least squares fit of $P = e^{At+B}$ (T = −1/A) from the moment of pk−dP/dt to the opening of the mitral valve.[6] The opening of the mitral valve was defined from the angiographic frame preceding that in which non-opacified blood first entered the left ventricle. In all cases mitral valve opening was identified in the same frame by two independent observers.[6]

ANALYSIS OF GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION DURING SYSTOLE AND DIASTOLE
From all cineangiograms one complete cardiac cycle was analysed frame by frame. Films were projected with a 35 mm film projector and converted into video format with a video camera‡. The ventricular contour was detected automatically with a dedicated hard

wired system.[7] Left ventricular volume was computed according to Simpson's rule for each frame. Stroke volume, global ejection fraction, and total cardiac index were determined. End-diastole was defined as the moment when the derivative of left ventricular pressure first exceeded 200 mmHg/s. In all cases this point coincided with the maximal measured volume. End-systole was defined at the occurrence of the incisura of the central aortic pressure, recorded with a tip-manometer on a 5F catheter*. Early diastole was defined as the interval between the opening of the mitral valve and minimal ventricular diastolic pressure. Early diastolic left ventricular inflow volume was measured as an absolute value (ml), and early diastolic mean inflow rate was calculated as the ratio between the difference of ventricular volumes at minimal pressure and opening of the mitral valve and the time interval corresponding to the number of frames between them.

To analyse regional left ventricular function, a system of 20 co-ordinates is generated[7] along which the left ventricular displacement is determined frame by frame (Fig. 1).

The orientation of the 20 co-ordinate axes was originally developed from the motion of these endocardial sites in normal subjects[7] and formulated in a generalised mathematical expression amenable to automatic data processing.

Regional wall velocity was computed as the first derivative of the instantaneous displacement function. Mean wall velocity (V̄) was calculated from end-diastole to end-systole (Fig. 1).

To express quantitatively the contribution of a particular segment to global ejection fraction, segmental volume was computed from the local radius and the height of each segment and indexed for end-diastolic volume (Fig. 2). This was termed regional contribution to global ejection fraction. The sum of all 20 determinations equals the global ejection fraction. Diastolic pressure-volume relations were determined from the minimal diastolic pressure to the beginning of the "a" wave. The natural logarithm of pressure was used in a linear regression analysis of pressure and volume from which a slope k was derived. Changes in k were taken as changes in volume stiffness.[8]

CORONARY SINUS BLOOD FLOW MEASUREMENT AND MYOCARDIAL OXYGEN CONSUMPTION
In the second part of this study, the effect of intracoronary injection of nifedipine on coronary sinus blood flow and myocardial oxygen consumption was determined in 10 other patients (54 to 68 years), who all had significant coronary heart disease.

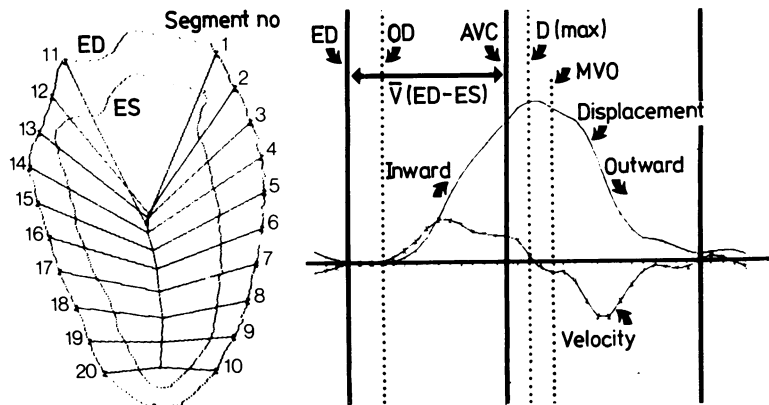Blood flow was measured via the continuous ther-

Fig. 1 *End-diastolic and end-systolic left ventricular contours, as detected with the automated analysis system. On these silhouettes is superimposed a system of co-ordinates along which segmental left ventricular wall displacement is detected. Left ventricular wall velocity—first derivative of wall displacement—is derived from these data. ED, end-diastole; ES, end-systole; OD, onset of displacement; $\overline{V}$ (ED–ES), mean systolic wall velocity; D (max), maximal inward wall displacement; MVO, mitral valve opening; AVC, aortic valve closure.*
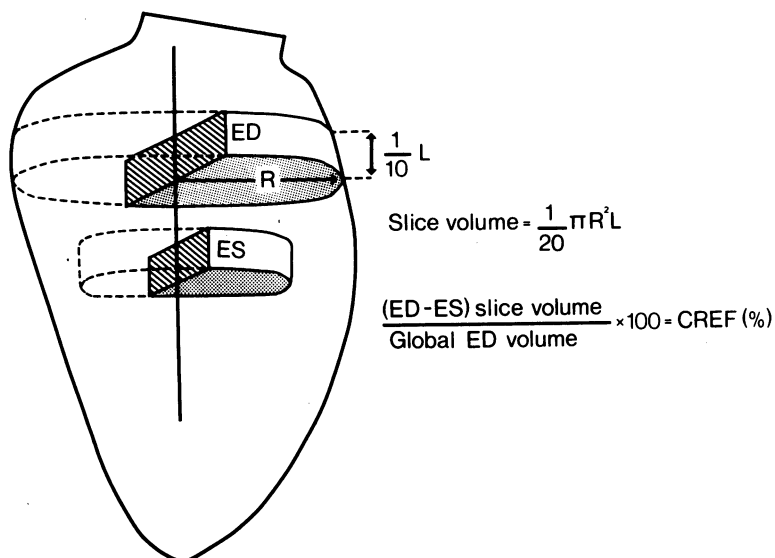

Fig. 2 *Method for computing regional contribution to ejection fraction (CREF): volume of each segment (slice volume) is computed according to the formula, shown in the Figure. The systolic volume change is normalised for left ventricular end-diastolic volume.*

modilution method of Ganz *et al.*[9] The position of the external thermistor was assessed by injection of 3 ml contrast material before the intracoronary injection of 0·1 mg nifedipine.

Before injecting nifedipine, the blood oxygen content in the aorta and in the coronary sinus was determined* and baseline data for flow and aortic pressures

*Lex-O-₂-CON, Lexington Instruments Corporation, Waltham, Mass., USA.

were obtained during 60 seconds. Thirty seconds and three minutes after the intracoronary administration of nifedipine these measurements were repeated and changes in myocardial oxygen consumption computed.

QUANTITATIVE CORONARY ANGIOGRAPHY

For the third part of the study, coronary artery dimensions were quantified in 12 patients (33 to 59

years), again catheterised for suspected coronary artery disease. Two patients had completely normal coronary arteries, one had single vessel disease, six had double vessel disease, and three had triple vessel disease, all with obstruction of 70% or more. The effects of intracoronary injection of nifedipine on coronary vasomotility were studied in four consecutive coronary cineangiograms. Before the angiographic study, a fibreoptic catheter* was inserted into the coronary sinus and the O_2 saturation was continuously measured.[10] The left ventricular pressure was also recorded continuously with a dual tip-manometer and analysed for changes in left ventricular contractility, reflected by peak dP/dt, peak V_{CE}, and V_{max}.[5] A total of 40 coronary segments was selected for quantitative angiographic analysis. Eight were stenotic in nature, five were prestenotic, 17 were poststenotic, and 10 were normal. Before injecting the nifedipine,

two baseline coronary angiograms (C1, C2) were performed five minutes apart. The second control angiogram (C2) was carried out to study the effect of the contrast agent itself on the artery. Five minutes later, 0·15 mg nifedipine was injected within 20 seconds into the left main coronary artery.

A third arteriogram (N1) was then obtained as soon as the coronary sinus saturation reached its maximum value, usually within 30 seconds. The final coronary angiogram (N2) was recorded when the coronary sinus saturation had returned to its control values, usually within five minutes. All arteriograms were obtained via the Sones technique and recorded on Kodak 35 mm cinefilm at the rate of 50 frames per second with the biplane Cardioskope U*. The contrast medium, 76% Urografin, was injected at a flow rate of 3 ml/s with a Medrad injector. To analyse a coronary segment, the 35 mm cinefilm is mounted on a
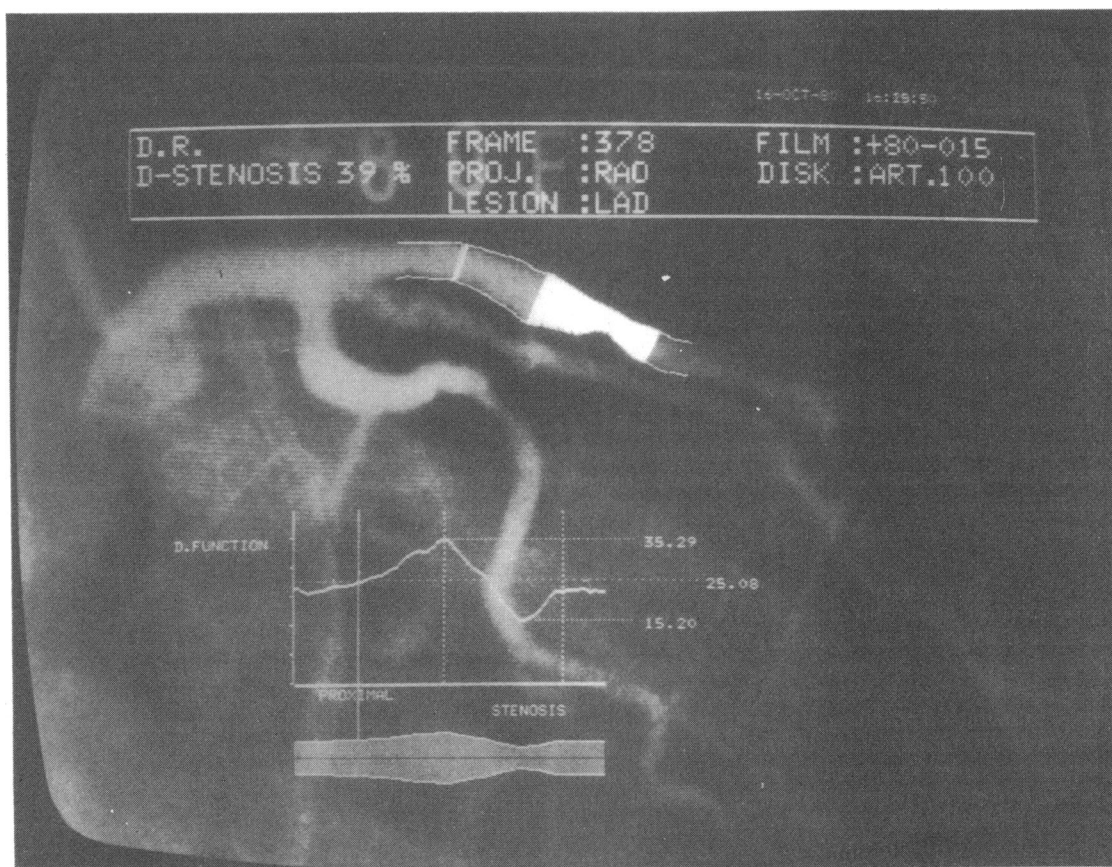
Fig. 3 *Cineangiogram of the left anterior descending coronary artery in the right anterior oblique projection. The detected contours are superimposed on the original video image. Administrative data are displayed at the top. The diameter function along this coronary segment is also displayed on the video screen.*

Table 1a *Left ventricular volume measurements and derived indices*

Case No.	Dose IC nifedipine (mg)	Heart rate/min		EDVI (ml/m²)		ESVI (ml/m²)		SI (ml/m²)		EF (%)	
		C	N	C	N	C	N	C	N	C	N
1	0·075	75	74	75·1	79·1	21·4	29·9	53·6	49·2	71·4	62·1
2	0·15	67	72	92	89·1	26·4	43·6	65·6	45·5	71·3	51
3	0·175	66	66	80·4	88·4	27·3	47·2	53·1	41·1	65·9	46·5
4	0·125	70	86	122·6	101·5	34·4	51·5	88·1	50	71·9	49·2
5	0·1	66	71	69·2	60·6	11·7	26·1	57·5	34·4	83	56·8
Mean		69	74	88	84	24	40	64	44	73	53
SD		±4	±7	±21	±15	±8	±11	±15	±6	±6	±6
p value		NS		NS		<0·002		<0·03		<0·005	

IC, intracoronary EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SI, stroke index; EF, ejection fraction; C, control; N, nifedipine.

Table 1b *Left ventricular pressure measurements and derived indices*

Case No.	P_{min} (mmHg)		k_p/ml		EDP (mmHg)		peak(+) dP/dt (mmHg/s)		peak VCE/s	
	C	N	C	N	C	N	C	N	C	N
1	0·3	6·5	0·125 r=0·88	0·045 r=0·96	8·7	17·4	1830	1460	47	39
2	6	13·1	0·029 r=0·97	0·007 r=0·72	20·8	23	1440	1110	29	24
3	1·4	14	0·048 r=0·97	0·012 r=0·97	9·9	21	1410	1020	36	20
4	0	13	0·061 r=0·96	0·031 r=0·97	12·1	22·8	1470	1130	38	25
5	0·3	8·1	0·158 r=0·89	0·049 r=0·98	10·4	21·6	1730	1020	54	22
Mean	1·6	11	0·084	0·029	12	21	1576	1148	41	26
SD	±2·5	±3	±0·054	±0·019	±5	±2	±191	±182	±10	±8
p value	<0·005		<0·03		<0·01		<0·005		<0·05	

P_{min}, left ventricular minimal diastolic pressure; k_n, slope of diastolic logarithmic pressure volume relation; EDP, end-diastolic pressure; dP/dt, rate of change of pressure. Values expressed as means ± SD.

Case No.	V_{max}/s		Peak LVP (mmHg)		ESP (mmHg)		TSR dyne s cm⁻⁵		Peak(−) dP/dt (mmHg/s)		TCR (ms)	
	C	N	C	N	C	N	C	N	C	N	C	N
1	59	50	138	132	71	70	1054	1137	2081	1454	35·4	60·8
2	41	31	98	91	79	59	879	962	1367	1073	51·5	70·3
3	41	26	101	95	81	59	1114	1180	1792	825	35·1	84·2
4	48	30	120	113	94	82	763	974	1520	1248	43·2	68·2
5	58	34	135	91	102	58	1364	1233	2164	1310	21·0	47·5
Mean	50	34	118	105	86	66	1035±231	1097±123	1785	1182	37	66
SD	±9	±9	±19	±18	±12	±10			±345	±242	±11	±13
p value	<0·005		NS		<0·05		NS		<0·02		<0·01	

TSR, total systemic resistance; VCE, velocity of contractile elements (dP/dt/P); V_{max}, VCE linearly extrapolated to P=0 mmHg; LVP, left ventricular pressure; ESP, pressure at aortic valve closure; TCR, time constant of relaxation; C, control; N, nifedipine.
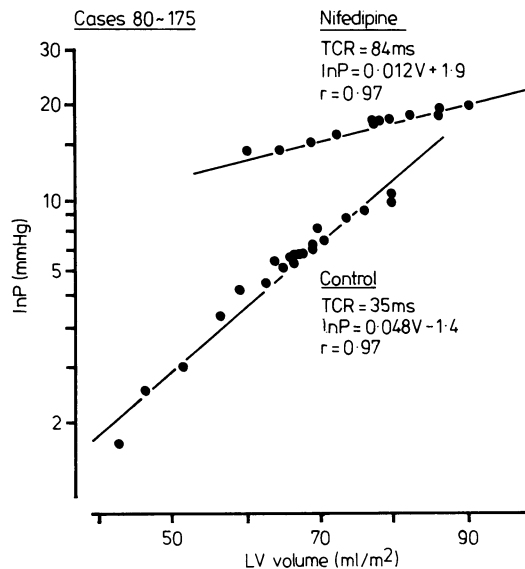
Cases 80~175

Fig. 4 *Pressure–volume relation during diastole before and after nifedipine. Linear regression equation of the relation between the natural logarithm of left ventricular pressure (ln P) and left ventricular volume is shown. Intracoronary nifedipine results in a reduction in the slope (kp) of the regression line. TCR, time constant of relaxation.*

Fig. 5 *Effect of nifedipine into the left main coronary artery on left ventricular anterior wall motion and its time sequence. Arrows indicate onset and the moment of maximal segmental wall displacement. Nifedipine induces a delay in onset of displacement, a decrease in the extent of segmental wall motion, and a delay in the maximal wall displacement. (A) Control left ventriculogram. (B) Left ventriculogram after nifedipine. ED, end-diastole; AVC; aortic valve closure.*
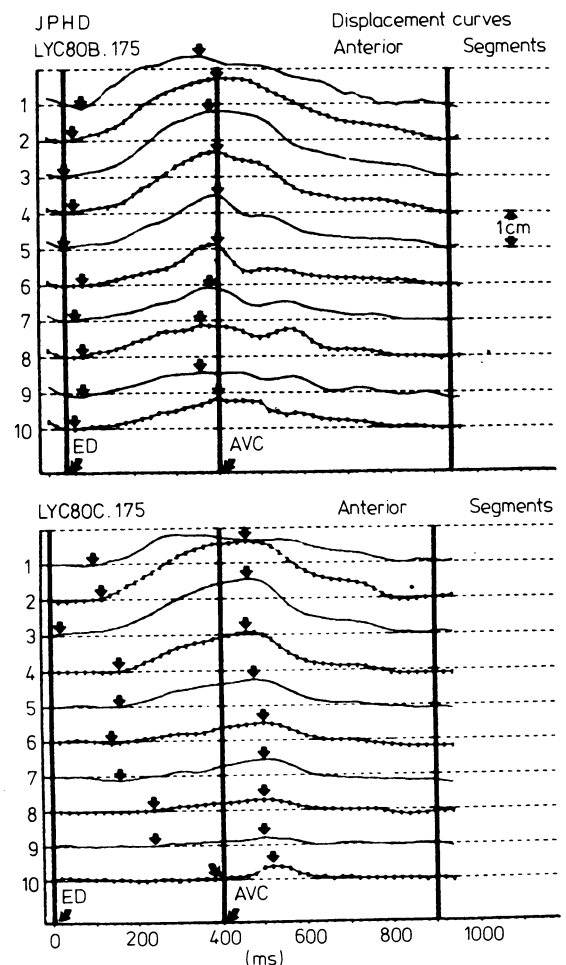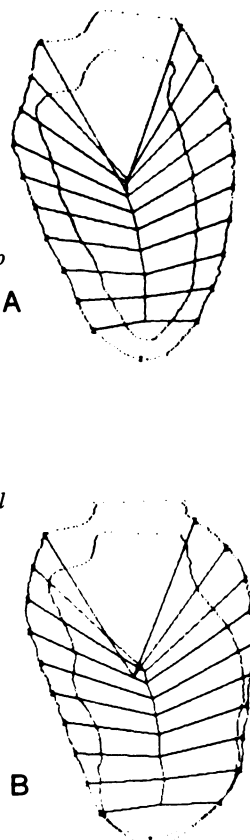
Table 2 *Regional contractile and pump function and time relation*

	Delay of onset of displacement (ms)		Relation between aortic valve closure and maximum wall displacement (ms)		$\bar{V}_{ED\text{-}ES}$ cm/s		CREF (%)	
	C	N	C	N	C	N	C	N
Anterior wall segments	29±27	144±95	−11±31	60±56	3·5±1·2	1·9±1·2	3·33±1·46	2·46±1·29
	p<0·0001		p<0·0001		p<0·0001		p<0·0001	
Inferior wall segments	28±27	72±70	10±44	22±76	3·5±1·1	2·3±1·0	3·32±1·34	2·85±1·26
	p<0·0001		NS		p<0·0001		p<0·0001	

C, control values; N, values 30 seconds after nifedipine; $\bar{V}$, mean velocity; ED, end-diastolic (based on pressure measurement); ES, end-systolic (based on pressure measurement); CREF, regional contribution to global ejection fraction. Values expressed as means ±SD; p, p value Student's t test (paired data).
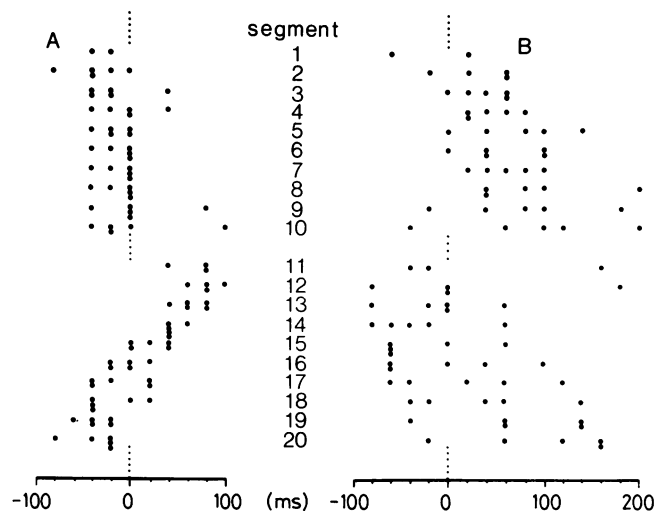

Fig. 6 *Time relation between aortic valve closure (time zero) and the occurrence of maximal wall displacement before (A) and after (B) intracoronary nifedipine. In 13 of 200 segments the moment of maximal wall displacement could not be determined accurately. These data are omitted in the figure.*

projector* and the selected frame converted into video format with a high resolution video camera for interactive computer processing.[11] The contours of the arterial segment are detected automatically by means of an averaging first derivative function applied to the digitised video brightness levels. The final output of the system for a segment of the left anterior descending artery in the right anterior oblique projection is shown in Fig. 3. From the detected contour positions a diameter function is computed which is also shown in Fig. 3.

To determine the mean diameter of a part of the processed arterial segment the user must indicate the boundaries of the part in question. It is emphasised that the x-ray system settings were not changed during consecutive filming after drug injection. Calibra-

tion of the diameter values in mm is, therefore, not necessary for comparative changes. The results after nifedipine administration are then expressed as relative changes in diameters, with respect to the control situation.

The accuracy and precision of the quantification method have been validated from cinefilms of copper models of obstructed coronary arteries with circular cross-sections suspended in 10 cm water. The accuracy was found to be 1·9% and the precision (variability) 1·6%.

Results

GLOBAL SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION
Left ventricular pressure and volume measurements before and 30 seconds after intracoronary nifedipine
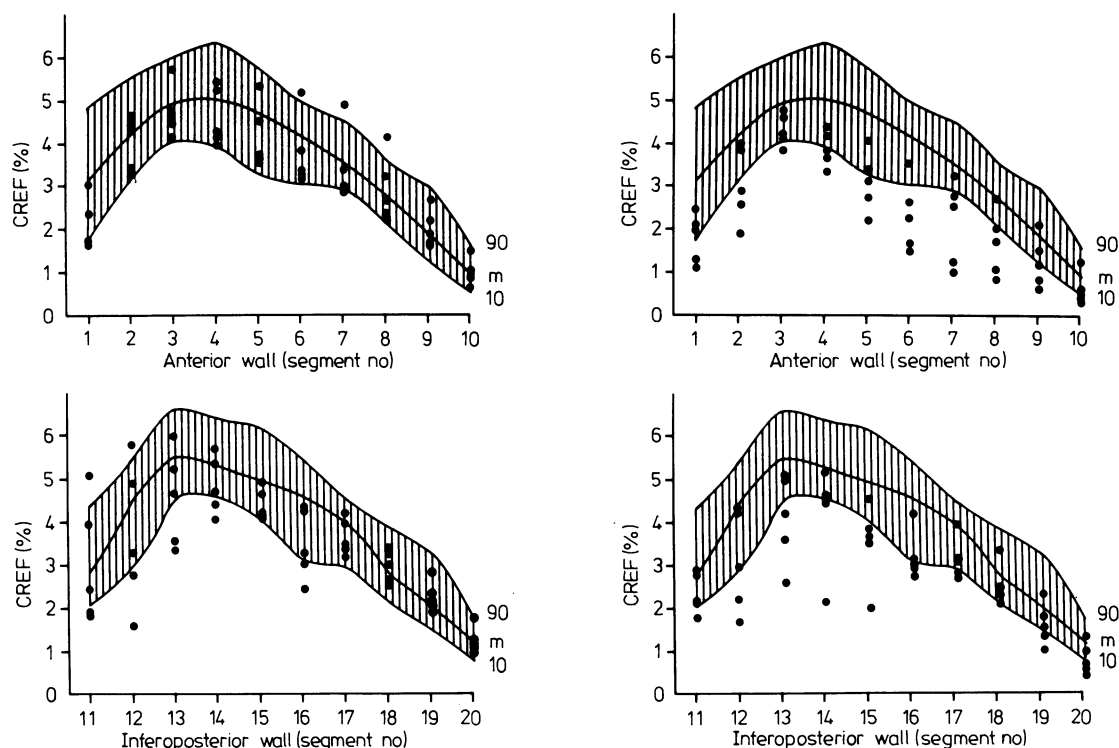
*Tage Arno.

Fig. 7   *Effect of nifedipine injection into the left main coronary artery on regional contribution to global ejection fraction (CREF). Left side of the Figure: individual CREF values (five patients) in the anterior and inferoposterior wall segments before nifedipine injection. Shaded areas represent the normal range of CREF values. Right side of the Figure: after nifedipine an overall depression of regional pump function is observed which is more pronounced in the anterior (segments 1–8) and apical (9, 10, 19, 20) areas.*

are shown in Table 1a and 1b. The heart rates remained essentially unchanged, while peak systolic pressure, peak positive dP/dt, peak negative dP/dt, and peak V_{CE} and V_{max} decreased significantly. In addition, the end-diastolic pressure became raised and the time constant of relaxation increased. End-diastolic volumes did not change significantly, but there was an increase in the end-systolic volume, with a consistent decrease in stroke index and thus ejection

fraction. Because of this decrease in cardiac output, and in spite of the transient reduction in blood pressure, the total systemic resistance remained unchanged. In four of five patients, the mean rate of flow, measured during the early diastolic filling period, between the mitral valve opening and the point of minimal pressure declined.

The relation between left ventricular diastolic pressure and volume after nifedipine is illustrated by one

Table 3   *Effect of intracoronary nifedipine (0·15 mg) on coronary sinus blood flow and myocardial oxygen consumption in 10 patients wit coronary artery disease*

	HR/min			Mean aortic pressure (mmHg)			CSBF (ml/min)		
	C	N1	N2	C	N1	N2	C	N1	N2
Mean	65	74	65	111	98	112	103	155	109
SD	±8	±8	±9	±13	±13	±10	±30	±40	±36
Cvs N1		p<0·002			p<0·0005			p<0·0005	
Cvs N2		NS			NS			NS	
Cvs N2		p<0·0005			p<0·0005			p<0·001	

C, control values; N1, values 30 seconds after nifedipine; N2, values 3 minutes after nifedipine; HR, heart rate; CSBF, coronary sinus blood flow; C coronary vascular resistance; (Ao–Cs) O_2, aortic/coronary sinus O_2 difference; MVO_2, myocardial oxygen consumption; p, p value Student's t test (pa data).

Values expressed as mean ± SD.

example (Fig. 4). It is evident that the entire diastolic pressure-volume relation is shifted so that, at any given volume, pressure is higher. This effect was consistently seen after each administration of nifedipine. The slope of the LnP vs volume line, however, (K)—an index of volume stiffness—was considerably reduced in all patients.

REGIONAL LEFT VENTRICULAR FUNCTION

The profound effect of intracoronary nifedipine on left ventricular wall motion and its time sequence is shown in Fig. 5. Before administration of nifedipine, displacement of the anterior and inferior wall was seen, 29 and 28 ms, respectively, after end-diastole (Table 2). After injection of nifedipine into the main stem of the left coronary artery, the onset of displacement of the anterior wall was delayed an additional 115 ms (p<0.001), while the inferior wall was delayed by 44 ms (p<0.001). For each segment the timing relation between aortic valve closure and the occurrence of the maximal wall displacement is shown in Fig. 6. Before nifedipine, the maximal displacement of the anterior wall occurred 11 ms before aortic valve closure. In contrast, with the anterior wall segments, the inferoposterior wall segments did not reach their maximal wall displacement synchronously. The maximal displacement of the five posterobasal segments (no. 11–15) occurred between 20 and 100 ms after aortic valve closure so that the maximal wall displacement of the entire inferior wall fell, on average, 10 ms after aortic valve closure. After nifedipine, the moment of maximal wall displacement for the anterior wall shifted from end-systole (11 ms before aortic valve closure) to early diastole (60 ms after aortic valve closure). The anterolateral and the apical segment of the anterior wall, as well as the apical segment of the inferior wall appear to be the most affected. On the contrary, the posterobasal wall segments reach their maximum in end-systole, instead of early diastole.

The measurement of mean systolic wall velocity after nifedipine showed a decrease which was again more pronounced in the anterior wall (Table 2) than in the inferior wall. The individual regional pump function data for all 20 segments before and after the intracoronary administration of nifedipine are given in Fig. 7. Though these data demonstrated a myocardial depression affecting the whole ventricle, the anterolateral and apical segments were most severely affected. Two patients with a dominant left coronary artery showed an impressive reduction of the pump function of their posterobasal wall segments as well. Under the influence of nifedipine, the mean values of regional contribution to global injection fraction decreased from 3·33 to 2·46% (p<0·0001) for the anterior wall and from 3·32 to 2·85% (p<0·0001) for the inferior wall.

CORONARY SINUS BLOOD FLOW AND MYOCARDIAL OXYGEN CONSUMPTION

Thirty seconds after intracoronary administration of nifedipine, coronary sinus blood flow increased significantly (p<0·005) from 103 ml/min to 155 ml/min but returned to the pre-administration values within three minutes (Table 3). Simultaneously, mean aortic blood pressure dropped from 111 mmHg to 98 mmHg then returned to control values. Despite this transient decrease in perfusion pressure, coronary vascular resistance was significantly reduced (1·15 versus 0·66 mmHg/ml per min; p<0·0002). Thirty seconds after nifedipine, the coronary sinus oxygen content almost doubled (from 6·0 to 11·9 ml/100 ml; p<0·0001), and this was reflected in a considerable narrowing of the aortic–coronary sinus oxygen difference (from 12·7 to 6·3 ml/100 ml; p<0·0001). In this group of patients, the net increase in myocardial blood flow was smaller than expected from the narrowing of the aortic–coronary sinus oxygen difference, reflecting a reduced myocardial oxygen consumption (from 13·4 to 9·6 ml/min; p<0·01).

QUANTITATIVE CORONARY CINEANGIOGRAPHY

Haemodynamic data assessing the effects of nifedipine on the epicardial coronary arteries are shown in Table 4. Peak systolic pressure remained constant during both control cineangiograms, but decreased by 14 mmHg immediately after the intracoronary injection of nifedipine (p<0·05). This acute change was transient so that by the time the

CVR (mmHg/ml per min)			(Ao–Cs) O_2 (ml/100 ml)			CS O_2 content (ml/100 ml)			MVO_2 (ml/min)		
C	N1	N2	C	N1	N2	C	N1	N2	C	N1	N2
1·15	0·66	1·12	12·7	6·3	11·9	6·0	11·9	6·6	13·4	9·6	13·7
±0·31	±0·15	±0·35	± 1·5	±1·6	±1·1	±1·1	± 1·4	±0·7	± 4·9	±3·1	± 6·1
	p<0·0002			p<0·0001			p<0·0001			p<0·01	
	NS			p<0·005			p<0·02			NS	
	p<0·0005			p<0·0001			p<0·0001			p<0·01	

Table 4 *Pressure derived variables and coronary sinus saturation during the two control (C1, C2) and the two post-nifedipine cineangiograms (N1, N2) (Mean ± SEM)*

	Peak LVSP (mmHg)	LVEDP mmHg	V_{max}/s	Peak dP/dt (mmHg/s)	Peak VCE/s	CS_{O_2} sat %
C1	135±11·5	18±2·6	47·8±2·3	1722±191	35·5±3·8	36 ±3·0
C2	137±11·6	19±2·6	45 ±2·10	1607±120	32 ±2·5	36 ±3·2
N1	123± 8·4	25±3·1	36·7±2·8	1333±139	24·3±2·4	63 ±4·7
N2	135±11	22±2·6	47·5±1·9	1629±139	31·3±2·6	35·3±1·1
C1 vs N1	p<0·05	p<0·002	p<0·005	p<0·02	p<0·02	p<0·01
C1 vs N2	NS	NS	NS	NS	NS	NS
C2 vs N1	p<0·005	p<0·001	p<0·002	p<0·05	p<0·01	p<0·005
C2 vs N2	NS	NS	NS	NS	NS	NS
N1 vs N2	p<0·03	NS	p<0·002	p<0·02	p<0·01	p<0·005

Abbreviations: Peak LVSP, peak left ventricle systolic pressure; LVEDP, left ventricle end-diastolic pressure; V_{max}, maximal velocity of contractile element; dP/dt, first derivative LV pressure; peak VCE, peak velocity of contractile element; CS_{O_2} sat, coronary sinus oxygen saturation; p, p value Student's t test (paired); NS, not significant.

fourth coronary angiogram was recorded, the left ventricular pressure had already returned to its control value of 135 mmHg. End-diastolic pressure showed a significant increase from 19 to 25 mmHg (p<0·001) 30 seconds after nifedipine had been administered. During the fourth cinefilm, the end-diastolic pressure was still slightly, but not significantly, raised. After the intracoronary injection of nifedipine, peak dP/dt and V_{max} decreased simultaneously by 17 and 18% and both variables returned to their control values by the time of the fourth coronary cineangiogram. As for the coronary sinus saturation, 30 seconds after the intracoronary administration of nifedipine there was a pronounced increase from 36% to 63% occurring simultaneously with the drop in V_{max}. It must be emphasised that five minutes after the intracoronary injection of nifedipine, there remained no detectable effect of nifedipine on the coronary sinus O_2 saturation or on contractility. The effects of nifedipine on the mean diameter of 10 normal, five prestenotic, and 16 poststenotic segments are given in Table 5 and shown in Fig. 8. One of the 17 poststenotic segments was excluded from the statistical analysis because it showed a paradoxical reduction of 60% in diameter after nifedipine. There is no significant difference in the mean diameter between the first and the second

control cinefilm. After administration of nifedipine (film N2), all segments (N=29) showed an increase of 12% (p<0·0001) in mean diameter, except for three coronary segments (one prestenotic, two poststenotic in series in the same artery).

These changes in detail were as follows. Thirty seconds after the intracoronary injection of nifedipine there was already a small, but significant vasodilatation (C1 vs N1, 6·2%, p<0·02; C2 vs N1, 7·9%, p<0·05) of the normal coronary segments. Five minutes later, on the last film (N2), there was an additional increase in mean diameter so that an overall increase of 10·3% (p<0·002) in mean diameter was observed between C1 and N2 and a 12·0% increase (p<0·001) between film C2 and N2. Similar changes were seen in the prestenotic coronary segments (Table 5).

Thirty seconds after nifedipine there was also a significant increase in the luminal diameter of the poststenotic segments (C1 vs N1, 8·3%, p<0·002 and C2 vs N1, 9%, p<0·001). This vasodilatation persisted and increased further: all 16 segments showed an increase in mean diameter with an average of 15·7% (p<0·0001) between films C1 and N2 and an average increase of 16·4% (p<0·0001) between films C2 and N2. Seven of the eight stenotic areas also

Table 5 *Effect of intracoronary nifedipine on mean diameter of normal, prestenotic, and poststenotic coronary segments; percentage diameter change is defined as: $(B-A)/A \times 100$*

A		B	Normal segment n=10 $\bar{m}±SD$ %	p	Prestenotic segment n=5 $\bar{m}±SD$ %	p	Poststenotic segment n=16 $\bar{m}±SD$ %	p
C1	vs	C2	− 2±6	NS	+ 1± 4	NS	− 1± 7	NS
C1	vs	N1	+ 6±6	0·02	+ 6± 4	0·04	+ 8±10	<0·002
C1	vs	N2	+10±7	0·002	+10±10	NS	+16±11	<0·0001
C2	vs	N1	+ 8±6	0·05	+ 5± 4	NS	+ 9±10	<0·001
C2	vs	N2	+12±7	0·001	+ 9±10	NS	+16±11	<0·0001
N1	vs	N2	+ 4±7	NS	+ 4±10	NS	+ 8±11	<0·0005

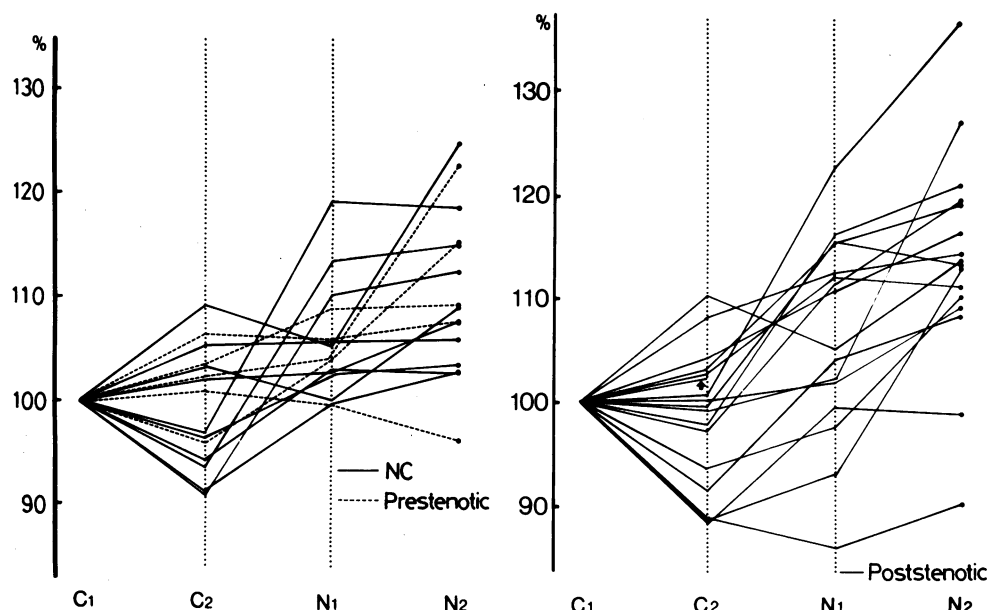p, p value, Student's t test (paired data).

Fig. 8 *Effect of intracoronary nifedipine on the mean diameter of 10 normal (NC), five prestenotic, 17 poststenotic coronary segments during two control cineangiograms (C1, C2), and two cineangiograms after nifedipine (N1, N2). The individual diameter measurements are expressed as percentages with respect to C1 = 100%. Arrow indicates a segment which shows paradoxical reduction of 60% after nifedipine injection (see text).*

dilated with nifedipine and their luminal diameters increased in absolute terms over a range of 4 to 30% (Table 6). There was a slight reduction in diameter in one segment.

It is clear that the normal, prestenotic, stenotic, and poststenotic segments remained in a state of vasodilatation even when V_{max} and the coronary sinus saturation had returned to their control values. In other words, nifedipine provokes a coronary vasodilatation which persists after the disappearance of its direct effects on the myocardium.

Table 6 *Luminal diameters of eight stenotic lesions during control cineangiogram (C1) and after (N2) intracoronary administration of nifedipine; luminal diameters are expressed in pixels*

Control C1	Nifedipine N2	Luminal diameter change %
4·73	6·18	31
9·92	12·59	27
10·93	13·67	25
10·31	12·63	22·5
13·75	16·10	17
13·97	15·29	9·4
8·32	8·68	4·3
9·84	8·90	−9·5

Luminal diameter change is defined as: $(N-C)/C \times 100$, and expressed as a percentage.

Discussion

GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION

Earlier studies of the direct effect of nifedipine on the myocardium were carried out in this laboratory in patients in whom radiopaque markers had been implanted on the epicardium at the time of bypass surgery.[12]

The question remained, however, to what extent regional endocardial movement was affected. In order to investigate this aspect, frame by frame analysis of the left ventricular cavity outline provided the opportunity to investigate the relation between changes in regional endocardial wall motion and alterations in left ventricular isovolumic contraction and relaxation, which have been described after intracoronary administration of nifedipine.[13]

Asynchrony in regional wall motion in itself could explain the disturbance in isovolumic contraction, the depressed systolic function, and the abnormalities in relaxation.[14 15] In other words, the teamwork which must exist between the different parts of a ventricle to provide maximal mechanical efficiency during ejection might be simply disrupted by the regional administration of nifedipine, without implying a true reduction in regional myocardial performance. It has
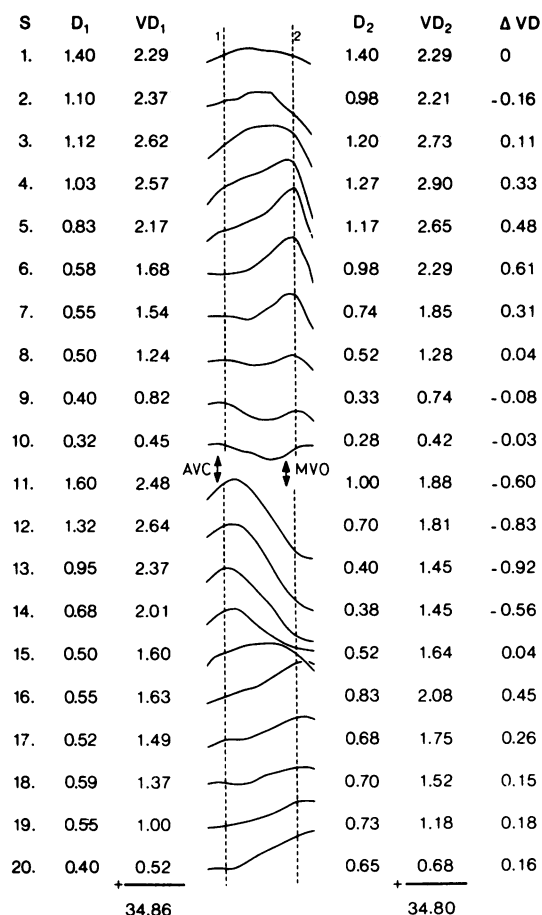
S	D_1	VD_1		D_2	VD_2	ΔVD
1.	1.40	2.29		1.40	2.29	0
2.	1.10	2.37		0.98	2.21	-0.16
3.	1.12	2.62		1.20	2.73	0.11
4.	1.03	2.57		1.27	2.90	0.33
5.	0.83	2.17		1.17	2.65	0.48
6.	0.58	1.68		0.98	2.29	0.61
7.	0.55	1.54		0.74	1.85	0.31
8.	0.50	1.24		0.52	1.28	0.04
9.	0.40	0.82		0.33	0.74	-0.08
10.	0.32	0.45		0.28	0.42	-0.03
11.	1.60	2.48		1.00	1.88	-0.60
12.	1.32	2.64		0.70	1.81	-0.83
13.	0.95	2.37		0.40	1.45	-0.92
14.	0.68	2.01		0.38	1.45	-0.56
15.	0.50	1.60		0.52	1.64	0.04
16.	0.55	1.63		0.83	2.08	0.45
17.	0.52	1.49		0.68	1.75	0.26
18.	0.59	1.37		0.70	1.52	0.15
19.	0.55	1.00		0.73	1.18	0.18
20.	0.40	0.52		0.65	0.68	0.16
		34.86			34.80	

AVC MVO

Fig. 9 *Segmental wall motion after intracoronary nifedipine during the isovolumic relaxation phase, between the closure of the aortic valve (AVC) and the opening of the mitral valve (MVO). See also Fig. 1. S: segment number; D1: segmental wall displacement (cm) between end-diastole (ED) and AVC; D2: segmental wall displacement (cm) between ED and MVO; VD1: segmental volume displacement (ml) between ED and AVC; VD2: segmental volume displacement (ml) between ED and MVO; Δ VD: changes in segmental volume between AVC and MVO, expressed in ml.*

been suggested that the primary abnormality induced by intracoronary nifedipine could be a delayed onset of contraction without abnormal function. If this theory was correct, all disturbances described above could be the result of an electrophysiological delay in the activation of the Purkinje fibres, but recent work of Dangman and Hoffman[16] showing that has all but excluded this possibility. It is more likely that the changes in isovolumic contraction and relaxation reflect either globally altered myocardial contractility or asynchrony of the electromechanical coupling within the sarcomere population. The data obtained from the analysis of endocardial wall motion favour the former hypothesis. A delay in the onset of wall displacement (Table 2) and a profound change in the timing relation between aortic valve closure and peak inward displacement of the individual wall segments were clearly shown. Normally, contraction ends in a synchronous manner, except for some physiological late contraction of the inferobasal area (Fig. 6). After nifedipine a considerable delay (Table 2) of the

anterior segments (4–8) and apical segments (8–10, 18–20) was seen, while contraction of the inferobasal segments (11–15) ended earlier. The mean velocity of systolic wall displacement ($\overline{V}_{ED-ES}$) was significantly reduced (Table 2). Furthermore, after intracoronary administration of nifedipine, regional contribution to ejection fraction of the anterior and inferior wall segments decreased, respectively, by 26 and 14%.

Intracoronary nifedipine not only slows and depresses the segmental contraction, but also delays and prolongs it.

This latter observation led us to analyse another phenomenon. Since the volume of the ventricle is, by definition, constant during the relaxation period— defined in terms of valve movement—inward movement in one area must be compensated for by outward movement elsewhere. This is illustrated and shown quantitatively in Fig. 9. Displacement 1 (D_1) expresses for the individual segments the systolic inward wall displacement from end-diastole to aortic valve closure. Between aortic valve closure and mitral valve

opening the majority of the anterior and inferoapical segments show a persisting inward wall motion, in contrast with the inferobasal segments which move outward. Column D_2 (displacement 2) expresses the net effect of inward and outward wall displacement as computed just before mitral valve opening.

From the displacement D_1 and D_2 the segmental volume displacements are computed. The total volume displaced between end-diastole and aortic valve opening equals that displaced between end-diastole and mitral valve opening. Thus, the ventricular volume remains constant while a variety of segmental wall motion changes takes place. In studying this illustration it becomes obvious that changes in the rate of pressure relaxation may not only reflect a globally altered myocardial relaxation but also heterogeneity in activation and performance within the sarcomere population, with continuation of contraction and tension development extending into the isovolumic period. In other words, impaired relaxation of the ventricle as a whole must not automatically be equated with impaired relaxation at a cellular level.

Fleckenstein *et al.*[17] have indicated that electromechanical decoupling occurs after nifedipine which leads to a decrease in actin-myosin interaction. The negative inotropic effect on the heart which was recorded and the upward shift in left ventricular diastolic pressure volume curves observed in this study are probably an expression of that fundamental biochemical effect: nifedipine interrupts the normal process by which calcium is transported to the cell, lowers the cytosolic calcium, and inhibits and delays contraction of the myocardial wall so that there is delay in diastolic interaction of contractile elements. This could be a reasonable explanation for the upward shift in left ventricular diastolic pressure volume curves. On the other hand, residual diastolic interaction between contractile elements—caused by an increased cytosolic calcium[18]—has also been proposed as a possible explanation for the upward shift in diastolic pressure volume relations seen during angina.[19][20]

Cultures of dissociated beating ventricular cells from chick embryos manifested a negative inotropic response to calcium antagonism.[21] That is, amplitude and velocity of contraction of the individual cells decreased in the presence of the drug, while there was no effect on velocity of cell wall motion during relaxation. Higher calcium concentrations, however, did cause a slowing in the rate of relaxation and a decrease in the amplitude of contraction as though the cells were in a constant state of partial contracture. Thus, the apparently conflicting observations are reconciled since the changes induced in cultured cells by high calcium concentrations are reversed by calcium antagonists, indicating "that calcium antagonist can dramatically improve systolic and diastolic function of

a calcium-overloaded myocardial cell".

CORONARY BLOOD FLOW AND MYOCARDIAL OXYGEN CONSUMPTION

In our patients the myocardial oxygen consumption decreased by 28% after intracoronary injection of nifedipine. From our haemodynamic and angiographic data we assume that the decrease in myocardial oxygen consumption depended primarily on a decrease in contractility and left ventricular performance. This interpretation, however, is open to question, since despite an increase in global coronary blood flow, a decrease in endocardial flow and oxygen supply could make the endocardium ischaemic and consequently alter its mechanical performance. Others have pointed to the fact that after administration of a coronary vasodilator endocardial capillary blood flow may actually decrease because of an epicardial coronary "steal" phenomenon.[22]

This difference in regional blood flow response is seen particularly when coronary blood flow is increased in the presence of a critical stenosis of a large coronary artery.[23][24] In these circumstances, when flow is increased as a result of arteriolar dilatation distal to the stenosis, transmural perfusion becomes heterogeneous because of the greater increase in epicardial flow.[25] In the present study we do not have any experimental evidence which would allow us to rule out this possibility, but Henry *et al.*[26] have shown that, in dogs subjected to coronary occlusion, nifedipine increases collateral flow to the ischaemic myocardium. This increase was accompanied by a relative increase in endocardial perfusion, a phenomenon that was particularly prominent in the ischaemic zone.[26]

QUANTITATIVE CORONARY ANGIOGRAPHY

Although it has been proved that nifedipine dilates the coronary arteries, particularly in patients with variant angina, there have been few reports showing whether this drug actually dilates the coronary artery at the point of the stenotic lesions or at points distal to fixed obstructions.[27]

The present study provides quantitative measurements of the effects of nifedipine on the epicardial coronary artery after direct intracoronary administration. This route of administration was used in order to dissociate its coronary vasodilator action from its direct myocardial effect and afterload reduction.[12][28] When nifedipine (0·1 mg) was intravenously injected, it had no detectable haemodynamic effects. When nifedipine was regionally administered, it had a transient negative inotropic effect, associated with a transient increase in coronary blood flow and decrease in myocardial oxygen consumption. The vasodilatation of all three, the prestenotic, stenotic, and poststenotic

coronary segments, persisted, however, much longer than the haemodynamic effects, at least during the period of observation in this study. This observation raises the possibility that there are distinct differences in the response to nifedipine between the myocardial cells and the smooth muscle cells in the coronary vascular wall.

Another essential question is: what effect do large vessel vasomotor tone and distal arteriolar resistance have on a proximal lesion? In isolated perfused human coronary arteries, a decrease in perfusion pressure can lead to a "dynamic" increase in resistance to flow across an elastic and eccentric stenosis.[29]

The study has even shown experimentally that the administration of a coronary vasodilator could induce a fall into distending pressure of the poststenotic coronary segment, resulting in a passive collapse of the wall of the stenotic segment and an increase in resistance to flow.[30-32]

An explanation for these conflicting possibilities may be that in the experimental studies the vasodilators affected primarily the distal arteriolar coronary bed leading to a reduction in poststenotic intraluminal pressure, whereas in the clinical studies the epicardial large coronary arteries were primarily affected in their prestenotic as well as in their poststenotic segment.[33]

Conclusion

Intracoronary nifedipine not only delays and prolongs the segmental contraction, but also slows and depresses it. It is suggested that a decreased cytosolic calcium might induce delayed diastolic interaction between contractile elements which could be a reasonable explanation for alteration of the isovolumic relaxation and for the upward shift in the left ventricular pressure volume curve after intracoronary administration of nifedipine. We presume that the decrease in myocardial oxygen consumption depends primarily on a decrease in contractility and left ventricular performance. Finally, we showed that the vasodilatation of the epicardial vessels after intracoronary nifedipine persists longer than its direct effects on the myocardium. In conclusion, the transient regional "cardioplegic" effect of nifedipine, associated with an increase in coronary blood flow, a reduction in MVO_2, and a vasodilatation of the epicardial vessels, is likely to be beneficial during temporary coronary occlusion.

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